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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/527,352	03/17/2000	Edward L. LeCluyse	421/17.2	3016

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JENKINS & WILSON, PA
3100 TOWER BLVD
SUITE 1400
DURHAM, NC 27707

EXAMINER	
AFREMOVA, VERA	
ART UNIT	PAPER NUMBER
1651	9

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/527,352	LeCruse et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 17, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-66* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other.

DETAILED ACTION

Claims 1-64 as amended and new claims 65 and 66 are pending [Paper No. 7 filed 9/17/2001].

Response to Arguments

Applicant's arguments filed 9/17/2001 have been fully considered but they are not persuasive for the reasons below.

Claim Rejections - 35 U.S.C. § 112

Claims 1-24 and 39-66 as amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 13, 39 and 52 as amended are rendered indefinite by the phrase "normalized" amount because it is uncertain what is encompasses by these "normalized" amounts and how these amounts are normalized or determined. The metes and bounds of the claims can not be determined as claimed and as disclosed.

Claim Rejections - 35 U.S.C. § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-11, 13-23 and 25-38 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by LeCluyse et al. [U] or Liu et al [IDS-EE] as explained in the prior office action and for the reasons below.

The claims as explained in the prior office action. The claims are directed to a method of screening a candidate compound or a plurality of candidate compounds for susceptibility to biliary excretion wherein the method comprises step of providing a sandwich culture of hepatocytes with one bile canaliculus or with a canalicular network, step of exposing candidate compound(s) to the sandwich culture and step of determining amount of the candidate compound(s) in the bile canaliculus or within the canalicular network. Some claims are drawn to the method of screening comprising additional step of washing the culture and using candidate compound with radiolabeled or fluorescent marker. Some claims are further drawn to the use of rat hepatocytes, to the use of long-term hepatocyte culture, to the use of collagen for the sandwich culture matrix in the method of screening candidate compounds.

The references are relied upon as explained in the prior office action.

With respect of the claim 1-11 and 13-23 applicants' argument that the cited references by LeCluyse et al. [U] or Liu et al [IDS-EE] do not teach determination of "normalized" amounts in order to facilitate extrapolation of experimental observation is not convincing since it is uncertain what are the "normalized' amounts as intended. The applicants' disclosure on the cited specification at page 30 for the support of argument does not appear to teach a facilitation as argued. Although the phase "normalized" has a literal support for the present amendment, the meaning of the "normalized" amounts in the context is uncertain and it has been interpreted as standard consideration of concentration parameters used in the art.

With respect to the claims 25-38 applicants' argument is not convincing because the use of identical fluorescent marker compound (carboxyfluorescein (CF), for example) as the applicants' cited marker (page 23) is taught in the method of LeCluyse et al. [U] drawn to screening a candidate compound (CFDA, for example) wherein the method of the cited reference encompasses the same steps as presently claimed method including exposure of hepatocytes culture to both marker and candidate compounds at least during some period of culturing hepatocytes. Thus, whatever differences in biliary excretion for both marker and candidate compounds might exist, the method of the cited reference does not appear to be different from the presently claimed method. And the method of Liu et al [IDS-EE] encompasses evaluation of uptake and excretion of several compounds including markers and/or radiolabeled compounds. Thus, whatever differences in biliary excretion between marker and candidate compounds might be intended the method of the cited reference does not appear to be different from the claimed method.

Claims 39-64 remain rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. [IDS-CC].

The claims are directed to a method of *in vitro* screening a candidate compound for susceptibility to *in vivo* biliary excretion wherein the method comprises step of providing a sandwich culture of hepatocytes with a canalicular network, step of exposing candidate compound to the sandwich culture, step of determining amount of the candidate compound in

within the canalicular network and step of determining a biliary clearance value for candidate compound. Some claims are drawn to the method of screening comprising additional step of washing the culture and using candidate compound with radiolabeled or fluorescent marker. Some claims are further drawn to the use of rat hepatocytes, to the use of long-term hepatocyte culture, to the use of collagen for the sandwich culture matrix in the method of screening candidate compounds. Some claims are drawn to additional steps of washing and/or lysing the culture and to determining amounts of metabolite of the parent candidate compound exposed to the culture.

The cited reference is relied upon as explained in the prior office action.

The rejection of the claims 1-38 under 35 U.S.C. 102(a) as being anticipated by Liu et al. [IDS-CC] has been withdrawn in the light of Declaration under 37 CFR § 1.131 which provides the evidence (Exhibit A) that the subject matter of the instant claims 1-38 was invented prior to the date of the cited reference by Liu et al. [IDS-CC] as demonstrated by the subject matter disclosed in the Exhibit A.

However, the disclosure of the Exhibit A does not appear to contain subject matter which is encompassed by the instant claims 39-64 such as an *in vitro* evaluation of "biliary clearance" of a candidate compound in the culture of hepatocytes, for example. Therefore, the claims 39-64 remain rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. [IDS-CC].

hepatocytes has metabolic function of the liver in vivo (col.8, line 23) and that the sandwich culture is suitable for studying hepatocyte metabolism and recovering product of hepatocyte metabolism (col. 8, line 33). In addition, the cited patent suggests various extracellular matrix components (col. 8, lines 38-41).

The primary references LeCluyse et al. [U] and Liu et al [IDS-EE] appear to lack the particular disclosure related to determining a specific value such as "biliary clearance value" for candidate compound released into bili canaliculi.

The secondary reference by Liu et al. [IDS-DD] discloses method of screening candidate compound taurocholate (TC) for susceptibility to biliary excretion in sandwich culture of hepatocytes and suggests determining Km and Vmax values for examining activity and regulation of hepatobiliary transport systems.

The secondary reference by Poole et al. [U] discloses method of screening candidate compound thyroxine T4 for susceptibility to biliary excretion *in vivo* and in the culture of hepatocytes and teaches direct correlation for the *in vivo* biliary clearance value for thyroxine and the *in vitro* accumulation of thyroxine.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the methods of screening candidate compounds for susceptibility to biliary excretion of the primary references [U] and [IDS-EE] by determining the values related to biliary excretion of candidate compounds as suggested by the secondary references [IDS-DD] and [U] with a reasonable expectation of success in investigating

susceptibility of candidate compound or drug interaction relevant to biliary excretion because the sandwich culture of hepatocytes is known to have metabolic functions of the liver *in vivo* and several various and specific parameters have been suggested in the prior art for evaluation and comparison of biliary clearance or biliary excretion of test compounds the *in vitro* and the *in vivo* systems.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

With regard to the cited references by LeCluyse et al. [U] and by Liu et al [IDS-EE] applicants' argument is repetitive and it has been discussed above as related to indefiniteness of the phrase "normalized" amounts.

With regard to the cited US'026 (Dunn et al.) applicants argue that the teaching of the cited reference is not tantamount to the subject matter of the present invention. However, the cited reference was/is relied upon to demonstrate that the sandwiches cultures are suitable for both animal and human hepatocytes as required by at least some of the claims.

With regard to the cited reference by Poole et al. [U] applicants' argument that the cited method does not ultimately benefit human beings is not well taken since both the presently

claimed method and the method of the cited reference are directed to screening of candidate compounds rather than administration of candidate compounds.

With regard to the cited references by Liu et al. [IDS-DD] and Liu et al. [IDS-CC] applicants' arguments drawn to abbreviated nature of the reference teaching or missing disclosure related to particular determination/calculation of biliary clearance value is promising. However, no argument/evidence has been presented that the particular determination of biliary clearance value as claimed and/or as intended by applicants is different from the cited prior art method of screening candidate compound *in vitro* for susceptibility of the candidate compound to *in vivo* biliary excretion.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

November 30, 2001.

SANDRA E. SAUCIER
PRIMARY EXAMINER

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